THE PRESENT VALUE OF THE WASSERMANN REACTION.

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In recent years one of the greatest advances in medicine has been marked by the adoption of the Wassermann reaction in the diagnosis and treatment of syphilis. It has necessitated extensive revision of many of the older conceptions of the disease. The definite relationship of syphilis to the so-called parasyphilitic lesions has been established. Further, it has proved of immense service in the differentiation of doubtful cases, such as ulcers, growths, various bone diseases, etc. Greatest of all, however, its value in the treatment of syphilis has been abundantly demonstrated, as it has provided a method by which the success or failure of therapeutic measures can be determined.

Even at the present time, however, different authorities report considerable variations in the results of this reaction. Its technique is being almost continually modified, and the exact interpretation that can be placed on its application to the diagnosis and treatment of syphilis is not yet sufficiently definite.

Even for normal individuals the results are disputed, an average being from 0.3 to 1.2 per cent. of positive cases, although Noguchi reports as high as 3.6 per cent. These figures, of course, depend on the class of cases examined, as many who eventually show definite syphilitic lesions give no history of the earlier stages of the disease.

In the primary stage of syphilis the number of positive reactions varies in the reports of different authorities from 64 to 92 per cent. It is certain, however, that in most cases a positive reaction can be obtained by the end of the fourth week, so a definite diagnosis can generally be had a week or two before the appearance of the secondary eruption. In about 40 per cent. of cases the Wassermann reaction is positive when the initial sore appears, and the number of positive reactions becomes progressively more frequent until the development of the secondary eruption, at which time over 90 per cent. are positive. The earliest occurrence is reported by Lesser, who found a positive reaction as early as the eighth day after exposure. In this case the initial lesion appeared fourteen days later, and was followed six weeks afterward by a typical roseola. In my experience in about 9 per cent. of cases where no treatment has been received the reaction did not become positive until the first or second week after the development of the secondary eruption. Clinical evidences seem to show that with the development of a positive Wassermann reaction there is general systemic invasion of the syphilitic virus.

Experimentally, it has also been demonstrated by Neisser that with the development of a positive reaction the lymphatic glands and other tissues of the body become capable of transmitting the disease to apes. As a rule therefore there is systemic invasion of the virus some time before the development of the secondary eruption, and in a large percentage even before the development of the initial sore.

In secondary syphilis, positive results are reported from 80 to 100 per cent. Indeed, one may say that practically every untreated case gives a positive reaction in this stage, although its appearance may occasionally be delayed until one or two or even three weeks after the appearance of the secondary eruption.

In the tertiary stage, positive reactions are reported in 60 to 100 per cent. of cases, but more correctly in about 80 per cent. The figures in this stage of the disease, although they vary considerably, depend chiefly on whether the syphilitic process is active or healed. Almost every active tertiary lesion is associated with a positive reaction.

The most constant results are undoubtedly in secondary and hereditary syphilis. In congenital cases almost all give a positive result, even at birth (95 per cent. or over). That this is of practical importance is obvious, as many children after birth develop snuffles, and a positive Wassermann reaction both confirms the diagnosis and indicates that active treatment should be instituted at once. It also assists therefore in clearing up the diagnosis of stillbirth and habitual abortion. In 56 per cent. or more of apparently healthy women, the mothers of syphilitic children, there is a positive reaction. Similarly, the children of syphilitic mothers are not immune to syphilis, but, as can be shown by the Wassermann reaction, are either syphilitic or healthy, or may later become infected. Thus a woman having given birth to a syphilitic child, and having a positive reaction, is to be considered as having latent syphilis, and should be given specific treatment. Also a positive reaction in the child of a syphilitic mother, even though the child looks healthy, indicates that it also ought to be treated.

Pregnant women who have had a previous history of repeated abortions or stillbirths, and who are found to have a positive reaction, should be given antisyphilitic treatment, and in this way healthy children may be born.

In relation to the choice of wet-nurses, the importance of this reaction is obvious.

After the clinical signs of syphilis have disappeared, many cases, although apparently in good health, remain in a latent syphilitic condition. Reports in this phase of syphilis average about 65 per cent. of positive reactions in the early latent stage, and as many as 47 per cent. in the late stages. These figures are naturally subject to the widest variation, as the treatment of syphilis has been so irregular in efficiency. Even in untreated cases it is difficult to estimate exactly how many will go on to a latent stage, and how long this may last, and whether it will lead to the late manifestations of syphilis, such as aneurysm, tabes, and paresis. By means of the Wassermann reaction the existence of latent syphilis may be recognized and adequate antisphyilitic treatment commenced. In this way the modern methods of treatment, which are guided by serum tests, have very materially lowered the percentage of cases of syphilis which have gone on to a latent stage, and so also of these latent cases which have eventually developed late syphilitic lesions.

In this latent stage of syphilis there may be no clinical manifestations which are obviously syphilitic, yet commonly such cases become extremely anemic, and often are the subjects of certain vague symptoms which usually disappear rapidly under antisyphilitic treatment.

It is not uncommon to find cases, even when treatment has been fairly thorough, where the reaction remains positive for ten or fifteen years after infection, and cases are reported positive after forty years. Undoubtedly many such latent cases become spontaneously cured, yet all are liable to develop further manifestations of syphilis.

Reinfection with syphilis occasionally occurs, particularly in cases which have been satisfactorily treated; but so far as I know in no case presenting at the time a positive reaction. Certainly apes resist the development of syphilis so long as the serum reaction remains positive.

In the late manifestations of syphilis, such as the so-called parasyphilitic lesions, perhaps more than in any other relation, the Wassermann reaction is called on for discriminating diagnostic tests, and is also of special use in indicating the line of treatment which may arrest the progress of the disease. The importance of any reaction which can aid in distinguishing a gumma from other forms of cerebral tumor is undisputed. Thus, as a general rule, no case of operation for cerebral tumor should ever be undertaken without a negative Wassermann reaction, and in all cases of epilepsy starting in adult life this reaction is also suggested.

Tabes and general paresis are not then parasyphilitic, but metasyphilitic or truly syphilitic lesions. This does not mean that all cases of tabes are syphilitic in origin, as undoubtedly ergotism, anemia, pellagra, and a great variety of other conditions are associated with a moderate degree of degeneration of the posterior columns of the spinal cord, and consequently may present some symptoms of ataxia. The fully developed, progressive type of the disease is, however, definitely syphilitic. As a general average in paresis, 81 per cent. in the blood serum and 85 per cent. in the spinal fluid, and in tabes 65 per cent. in the blood serum and 68 per cent. in the spinal fluid give positive results. In these cases it is the progressive types, with lymphocytosis in the spinal fluid, which furnish the positive reactions, while the stationary cases are generally negative. In cerebrospinal syphilis the reported results are rather conflicting, about 50 per cent. giving positive reactions in the blood serum and from none to 58 per cent. in the spinal fluid. It has been considered as a point of diagnostic importance that relatively few cases of cerebrospinal syphilis give positive reactions in the spinal fluid, yet when larger amounts of this fluid are used for the test, the positive reactions obtained closely follow the results in the blood serum. Cases of cerebrospinal syphilis usually give rather less frequent positive results than are found in tabes. Probably this is because many cases of cerebrospinal syphilis present only the results of the disease and not an actively syphilitic lesion. The examination of spinal fluid is valuable, as it gives very delicate reactions, although it does not seem to possess as much binding property as does the blood serum. It compensates for this, however, by not containing any complement, nor does it tend to develop anticomplementary actions in any way as extensively as occurs in blood serum. It therefore requires no devitalization, a process which considerably reduces the potency of the substances which produce a positive reaction.

It may well be wondered why any syphilitic infection can remain dormant in a spinal cord or other tissue and only after many years begin to produce its effect. Tubercle, however, may do the same thing, and some modifications in the subject's condition may be responsible for the sudden active development of the infective agent. Syphilis also may produce its effect slowly, and only after extensive damage are the lesions manifested clinically.

Other nervous diseases, such as amyotrophic lateral sclerosis, dementia præcox, disseminated sclerosis, syringomyelia, alcoholic psychosis, cerebral tumors, epilepsy, etc., are not related to syphilis, if one may judge by the negative reactions which they almost invariably present.

In diseases of the cardiovascular system, many questions at issue have been decided by this reaction. Cases of aneurysm, for instance, where the relation to syphilis has long been advocated, give positive reactions in about 70 per cent. of cases. It is also remarkable the frequency with which aortic incompetence is related to syphilis, as 72 per cent. are positive. Aortic incompetence in the majority of cases is syphilitic in origin, and therefore different in its etiology from mitral valve disease, in which the Wassermann reaction is generally negative. All other cardiovalvular lesions excepting aortic incompetence give only 24 per cent. of positive reactions. Even this latter figure undoubtedly shows the high incidence of cardiac disease in syphilis. Mesaortitis, or syphilitic aortitis, occurs in about 82 per cent. of paretics, but in only 10 per cent of all syphilitics, and this therefore is as truly a parasyphilitic lesion as tabes or paresis. It is the essential lesion which is the precursor of most cases of aortic aneurysm, as only few of such aneurysms result from the ordinary form of arteriosclerosis.

Of all cases of srteriosclerosis only about 12 per cent. give positive reactions, showing that this disease may be produced by many other factors even as common or more commonly than by syphilis; and also that aneurysm in nearly every case has a syphilitic basis.

When we find it reported that in all cases of keratitis, exclusive of suppurative cases, 84 per cent., in iritis 38 per cent., in retinitis and in choroiditis 26 per cent., give positive reactions (Leber), the importance of this test in diseases of the eye is evident, particularly as an indication for therapeutic measures. Similarly it has been shown that ozena is generally, but not always, of syphilitic origin.

Before any application of the serum test for syphilis is made in relation to the diagnosis and treatment of the disease, the general biologic principles involved in the reaction, as well as the method of technique, must be thoroughly appreciated. It is essentially a laboratory method, and is only of value in the hands of trained serologists, as there are innumerable possibilities of faulty technique which may materially modify the result. It is not the comparatively simple process it was originally conceived to be, supposedly depending on the union of a definite syphilitic and antisyphilitic, antigen and antibody, mixture. The first antigens used were derived from syphilitic tissue, yet it has been shown that fatty extracts from normal tissues are capable of giving similar results.

One of the more common factors responsible for the discrepancies in the percentage of positive cases is variation in the quality of the antigen employed, and it is still a debatable point what variety of antigen is the most specific. It is undoubted that the use of a correctly standardized antigen, thoroughly tested for its specific properties, and which in comparatively large amount is neither hemolytic nor anticomplementary, will largely increase the efficiency of the test. In my own experience I have used watery and alcoholic extracts of syphilitic liver, as well as similar extracts of normal tissues; but have found that fatty extracts fractionated by alcohol, ether, and acetone, according to the method advised by Noguchi, gave materially the most reliable results. Such fractionated antigens made from syphilitic liver and normal ox heart seemed of practically equal value in giving specific reactions. Many authorities, however, obtain the best results with extracts of syphilitic tissue. Antigens, as a rule, retain their properties for a considerable time, but after several months tend to deteriorate and become less specific.

The reaction then seems to depend on the development in the serum of syphilitic cases, of certain antilipoid substances, or, as has been suggested, of substances which have the power of destroying complement. It indicates, so far as can be determined, clinically and experimentally, an expression of the activity of the Spirochæta pallida, and is not therefore a true index of immunity against syphilis. The presence of antispirochete immune bodies can be determined by using an antigen made of spirochetes. The reactions obtained by lipoid and spirochete antigens do not quite correspond, as the latter is much more limited in its range of positive reactions, almost none being obtained in the primary stage, and only rarely in the secondary. Positive reactions obtained with pallida antigens are particularly obtained in latent and tertiary syphilis. They seem to follow more closely the results of the cutaneous reactions produced by luetin, which is an emulsion of dead spirochetes.

Although by no means such a source of variation in the results reported by different workers, as might occur from many other details of the technique of this reaction, the merits of the several hemolytic systems have occasioned considerable dispute. The only systems in common use are the human, sheep, and ox, and each has its adherents. I have used all three, and found no great variation in the results. The most difficult reactions to interpret have been in the use of the human system, and with this indicator there have been more doubtful results than with either of the other systems. Even with careful washing of the corpuscles in preparing the hemolytic amboceptor, a certain amount of precipitation seems to occur with certain serums, which may considerably obscure the result.

With the sheep system a clear cut reaction is usually obtained, yet with this also there are certain difficulties. In my series of reactions over 90 per cent. of human sera contained some natural antisheep hemolytic amboceptor. About 35 per cent. contained between one and two units in 2 c.c. serum, and over 50 per cent. contained more than two units. Most varied between two and four units, yet some contained as many as seven, twelve, or even twenty units. Any marked excess of hemolytic amboceptor will in many cases convert a weak yet truly positive into a negative reaction. It is important therefore to recognize that in nearly half the cases the addition of extra artificial antisheep hemolytic amboceptor is unnecessary, and would tend to increase the number of negative results, as the requisite two units are already contained in the serum. By standardizing this natural antisheep hemolytic amboceptor, contained so frequently in human sera, and where it exceeds two units, if the further addition of amboceptor be omitted about 9 per cent. more positive reactions will be obtained. These extra cases are those in which the specific agent in the serum was comparatively weak, yet they indicate definite evidence of syphilis, as can be substantiated clinically and by doing a parallel series with an ox system. The delicacy of the sheep system may still further be improved by removing all the natural antisheep amboceptor from the human serum, by saturation with sheep corpuscles until all the hemolysis possible has occurred. By this means the possibility of negative results being produced by sera containing over two units of natural antisheep amboceptor may be avoided.

Perhaps the most reliable indicator is the ox system. This has been used by Browning, Peters, and others, but for some reason or other has never been very extensively adopted. It has, however, many advantages, as only 1 or 2 per cent. or practically no human sera possess any natural anti-ox hemolytic amboceptor. It also gives clear-cut reactions, and judging from its parallel use with the other systems, and the support of clinical evidence, is in my experience at least, the most specific. In the use of this ox system there is one factor which must be recognized, that ox corpuscles require a much longer period for sensitization with their corresponding amboceptor than do the sheep or human corpuscles. Incubation of the amboceptor and corpuscle mixture at 37° C. for half an hour, however, generally insures complete sensitization.

The standardization of the complement, the recognition and the removal of anticomplementary bodies in the human sera, besides numerous other details of technique, make this reaction one of extreme delicacy and reliability. Too often, however, it is conducted without a thorough appreciation of the numerous possibilities of error, and it is probable that variations in the method technique, as well as differences in the class of cases examined, have largely been responsible for the discrepancies reported in the results of the Wassermann reaction.

Although the biologic principles involved are still more or less unknown, yet clinical experience had practically established this reaction as a reliable indication of syphilitic infection. The severity of the systemic infection can also to some extent be gauged by the estimation of the degree of the positive character of the reaction. If efficiently conducted it is almost specific, only very few other diseases being associated with positive reactions, and these irregularly. Cases of leprosy are credited with between 10 and 70 per cent. of positive reactions. Noguchi found it positive in 72.4 per cent. My own experience is limited to three cases, all of which were negative. In scarlet fever, also, reports vary extensively from 1 to 50 per cent., Swift finding 5 per cent. and Fua and Koch 12 per cent. In yaws and trypanosomias the Wassermann reaction is also described as frequently positive, so also in some occasional cases of anemia, tuberculosis, cancer, lymphadenoma, leukemia, etc. Since the discovery of the reaction, improvements in technique have, however, greatly improved the specificity of the reaction, and considerably fewer positive reactions are now obtained in other diseases than syphilis, so that for all practical purposes the finding of a positive reaction indicates a diagnosis of syphilis.

The value of a negative report, although important, is not quite so definite. A positive reaction may occasionally be delayed until the second week of the secondary stage. The disease may be the result of syphilis, yet exist in a healed condition where there is no spirochete activity. Occasionally also in some acutely syphilitic cases the serum may be negative, as if the spirochetes were not sufficiently active to produce a positive reaction. In such cases the diagnosis of syphilis does not have to stand on the report of the Wassermann reaction alone. A negative reaction may also be the result of recent treatment. Also the binding substances in the serum may be in such small amounts that the preliminary devitalization of the serum reduces them until they are insufficient to produce a positive reaction. Such weak reactions are commonly encountered in the late stages of treatment. Negative reactions may also be readily produced by imperfect technique.

As the greater certainty of the Wassermann reaction in its technique and specific relationship to syphilis has become more thoroughly established, the treatment of syphilis is now largely guided by the results of the serum tests, a positive reaction being held as indicating the presence of active spirochetes in the body. It has provided a method of making a certain diagnosis of syphilis in a much earlier stage than was formerly possible. Efficient treatment can therefore be commenced much sooner, when the disease is more readily influenced, and also with the natural result of lessening the possibility of future development of tertiary syphilitic lesions. Some few cases still seem to resist the most active treatment and develop tertiary lesions. Yet with the methods of treatment at present adopted, tertiary, latent, or late syphilitic manifestations should be eliminated. Certainly the longer the commencement of treatment is delayed the greater difficulty will be experienced in permanently removing a positive reaction from the serum, and until this is done the patient cannot be pronounced cured. It can be shown that even minute traces of mercury bichloride can destroy the binding substance in a syphilitic serum, *in vitro.* It is therefore not to be wondered at that even after short courses of treatment the number of positive reactions is greatly reduced. One negative result is then of little importance, especially if it occurs in course of treatment. If treatment is stopped the activity of the spirochetes recommences and a positive result can again be obtained. Repeated negative results, however, at intervals after the cessation of the treatment, indicate the probability of a final cure. A serum should not be examined for the Wassermann reaction before one month after the cessation of treatment, as negative results before this are of little importance. A negative result six months after the termination of the course of treatment would seem to indicate a cure. If, however, the reaction has again become positive an entire new course of treatment must be instituted. In latent cases, in which the reaction is recognized as positive some years after syphilis has been acquired, the treatment often has to be very vigorous and prolonged before the serum becomes permanently negative. An interesting finding, and one which is sometimes of use in doubtful cases, is that after an injection of salvarsan in a recently treated syphilitic presenting a negative reaction the serum may again become positive for a short time, as if the drug temporarily stirred up the activity of the spirochetes in the tissues. The time after which treatment causes the reaction in the serum of a syphilitic case to become negative varies with the severity of the case, the stage of the disease, and the extent of treatment. Sometimes two or three doses of mercury cause a temporary disappearance of the binding substance in the serum. In others very extensive treatment has to be pursued before the reaction becomes negative. The result of experimental and clinical experience seems to warrant the assumption that the appearance of a positive reaction in the serum is coincident with a systemic syphilitic infection. It indicates that treatment should be actively pursued, even though the subject is apparently in good health. It has therefore given a method by which a large percentage of the serious after-results of syphilis, such as aneurysm, aortic incompetence, tabes, paresis, keratitis, and the birth of syphilitic children, may be prevented.

Even if any such untoward results have occurred, there is now a considerable amount of evidence that their progressive character may be arrested by antisyphilitic treatment. Such damage to the bloodvessels as occurs in aneurysm or to the nervous system in tabes and paresis is of course permanent, but if the progression of these diseases can be stopped, then a great advance has been marked in their treatment. Also in the case of tabes, the undamaged portions of the cord may assume a considerable proportion of the functions which have been impaired by destruction of certain tracts. Thus reëducation exercises may largely improve the clinical condition of the subjects of this disease after its progressive character has been arrested. That some cases of late syphilis present negative reactions it is also of importance to recognize, as it prevents the indiscriminate administration of antisyphilitic treatment when the disease is already stationary and a healed process, and in which specific treatment would be of no avail.

The study of the Wassermann reaction in the last few years has shown that by the older methods of treating syphilis only in about one case in four was this successful.

Some cases were undoubtedly cured, in others treatment was unnecessarily prolonged, but in the majority the infection persisted and if the disease was not eventually eradicated by natural means, then late syphilitic manifestations were liable to occur.

The serum diagnosis of syphilis has demonstrated the inefficiency of mercurial treatment by internal administration. It has led to the discovery of the great tolerance which the intestine may acquire to this drug, so that after a time its only effect is to impair the nutrition of the patient. As Fordyce has stated: "Day after day we see patients the victims of paresis, tabes, etc., all giving identical therapeutic history of having had internal mercurial treatment for two or three years. The method stands condemned by its eloquent results."

It has shown the efficiency of treatment by salvarsan and neosalvarsan and also that combined with hypodermic injections of mercury salts; it is better than either alone. Although the hypodermic administration of mercurial preparations is greatly superior to internal treatment and may cause a very rapid disappearance of the external evidences of syphilis, yet only very slowly and often uncertainly, does it effect a cure, as judged by the frequent persistence of positive serum reactions.

With the aid of the Wassermann reaction syphilitic cases can be managed so that there is the least danger of relapses or the development of complications. It has therefore been one of the most important factors in the adoption of the present, earlier commenced, more rapidly effective, more certain, and more scientific methods of treatment.

DIAPHRAGMATIC HERNIA, WITH REPORT OF A CASE.

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Interest in diaphragmatic hernia has been greatly stimulated since the recognition of the condition has been so much facilitated by the development of Röntgen-ray technique. Although the lesion is not a remarkably rare one, until recently the diagnosis had but seldom been made, owing to the difficulty of correctly interpreting its physical signs. Grosser,[1] for example, in 1899, was able to collect records of 433 cases, but Arnsperger[2] makes the statement that up to 1908 the condition had been recognized during life in not more than 10 instances. Now, however, by

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[1] Wien. klin. Woch., 1899, No. 24, p. 655.

[2] Deutsch. Arch. f. klin. Med., 1908, xciii, 88.